

# Alzheimer's Disease and Inflammation Initiative

## 2001 Report

### *First Steps*

In 1995, Trustees of the Sir Zelman Cowen Fund, Professor Stone, convened a meeting of cognate scientists, to serve as a Scientific Advisory Committee<sup>1</sup>. The meeting considered, and supported, a proposal that the Fund's support for medical research should become focussed on a specific issue, the role of inflammation in Alzheimer's disease (AD). Minutes of this meeting and of subsequent meetings of these scientists, held in 1996 and 1997, show the stimulus for suggestion. Reports were appearing around the world which noted a relationship between long-term treatment with anti-inflammatory drugs, and the incidence of AD.

The earliest observations in this sequence were made in the UK, and in Sydney. The UK group<sup>2</sup> reported a negative correlation between chronic rheumatoid arthritis; it raised the question why AD was uncommon in those suffering arthritis. The Sydney group, headed by G.A. Broe at Concord Hospital (and part of the University of Sydney's Faculty of Medicine) noted the inverse relationship, that arthritis was uncommon among Alzheimer sufferers<sup>3</sup>

In the decade since, this seemingly obscure observation led to the broader hypothesis, that it was drugs taken by arthritis sufferers which provided protection against Alzheimer's disease. By the mid-1990's, the hypothesis that non-steroidal anti-inflammatory drugs (NSAIDS) are protective against AD was recognised as a potentially valuable hypothesis in the search for treatment for AD, though the idea had to fight for consideration and grant support with a growing range of scientific findings related to AD, concerning the tau and beta-amyloid proteins, and genetic causes, as for example in the alleles of the gene for apolipoprotein E. The Committee took the view that if inflammation does play a role in AD, and that NSAIDS are protective, this carried such potential benefit to at least those likely to develop AD, that it was an appropriate focus for SZCUF funding.

The Fund's *Alzheimer's Disease and Inflammation Initiative* was officially launched at a function in May 1996.

---

<sup>1</sup> Professor J.G. McLeod FAA FRS (Chairman)  
Professor Max Bennett B Eng, D Sc, FAA,  
Emeritus Professor William Burke BSc PhD,  
Professor Bogdan Dreher DSc  
Dr John Mc Avoy PhD  
Professor Ian Mc Closkey FAA, FTS, FRACP

<sup>2</sup> ML Jenkinson, MR Bliss, AT Brain, and DL Scott Rheumatoid arthritis and senile dementia of the Alzheimer's type *Rheumatology* 1989 28: 86b-88b

<sup>3</sup> Broe, G; Henderson, AS, and Creasey, H et al. A case-control study of Alzheimer's disease in Australia. *Neurology*. 1990; 40:1698-1707.

**Grants Funded under ADI Program****SZCUF GRANTS AND GRANTEEES 1996 - 2001****1996**

Dr Glenda Halliday	Inflammation and Alzheimer's Disease - Clinicopathological Correlations	\$ 30,000
Dr Jonathon Sedgwick	Microglial cell activation. Effect of anti-inflammatory agents and immunosuppressants.	\$ 17,711
Prof G A Broe	Anti-inflammatory Drugs and Alzheimer's Disease	\$ 52,194
Dr Philip Penfold	Microglia mediated cytotoxicity against neural cells: influence of bet-amyloid proteins	\$ 5,000
	1996 Total	<b>\$ 104,905</b>

**1997**

Drs Glenda Halliday & Jillian Kril	Is there a relationship between inflammatory and vascular pathologies and cognitive performance in prospectively studied patients with Alzheimer's disease?	\$ 47,500
Prof G A Broe	Anti-inflammatory Drugs and Alzheimer's Disease	\$ 42,000
Dr Philip Penfold	The Role of Microglia in Neuronal Cell Death	\$ 18,000
	1997 Total	<b>\$107,500</b>

**1998**

Dr Karen Cullen	Inflammation and microvascular degeneration in Alzheimer's disease: relationship to senile plaque progression and neurofibrillary degeneration	\$ 21,985
Dr Elizabeth Milward	Ant-inflammatory drugs: Regulators of oxidative damage in Alzheimer's disease?	\$ 50,000
	1998 Total	<b>\$ 71,985</b>

**1999**

Dr Karen Cullen	Inflammation and microvascular degeneration in Alzheimer's disease: relationship to senile plaque progression and neurofibrillary degeneration	\$ 21,985
Dr Jillian Krill	Genes regulating inflammatory processes and their role in dementia.	\$ 60,000
	1999 Total	<b>\$ 81,985</b>

**2000**

Dr Karen Cullen	Inflammation and microvascular degeneration in Alzheimer's disease: relationship to senile plaque progression and neurofibrillary degeneration	\$ 30,500
-----------------	--	-----------

**Total funding 1996-2000****\$396,875****Studies Reported**

The following publications have resulted from studies supported by the ADI

**Journal Articles**

1. **Waite**, LM; Broe, GA; Creasey, H; Grayson, DA; Cullen, JS; O'Toole, B.; Edelbrock, D., and Dobson, M. Neurodegenerative and other chronic disorders among people aged 75 years and over in the community. *Medical Journal of Australia*. 1997; 167:429-32.
2. **Whyte**, S; Brooks, WS; Grayson, DA; Creasey, H, and Broe, GA. Biochemical profile from the Sydney Older Persons Study Stage 3. *Aust NZ J Med*. 1998; 28:494.
3. **Milward**, EA; Grayson, DA; Creasey, H; Janu, MR; Brooks, WS, and Broe, GA Evidence for association of anaemia with vascular dementia. *NeuroReport*. 1999; 10:2377-2381.

4. **Broe, GA.**; Grayson, DA.; Creasey, HM.; Waite, LM.; Casey, BJ; Bennett, HP; Brooks, WS, and Halliday, GM. Anti-inflammatory drugs protect against Alzheimer disease at low doses. *Archives of Neurology*. 2000; 57:1586-91.
5. **Halliday, GM**; Shepherd, CE.; McCann, H.; Reid, WG; Grayson, DA; Broe, GA., and Kril, JJ. Effect of anti-inflammatory medications on neuropathological findings in Alzheimer disease. *Archives of Neurology*. 2000; 57:831-6.
6. **Penfold, PL**; Wen, L; Madigan, MC; Gillies, MC; King, NJC; Provis, JM. Triamcinolone acetonide modulates permeability and intercellular adhesion molecule-1 (ICAM-1) expression of the ECV304 cell line: implications for macular degeneration.
7. **Waite, LM**; Broe, GA; Grayson, DA, and Creasey, H. Motor function and disability in the dementias. *International Journal of Geriatric Psychiatry*. 2000; 15:987-903.
8. **Smith, MJ**; Kwok, JB.; McLean, CA; Kril, JJ.; Broe, GA.; Nicholson, GA.; Cappai, R; Hallupp, M.; Cotton, RG.; Masters, CL.; Schofield PR., and Brooks, WS. Variable phenotype of Alzheimer's disease with spastic paraparesis. *Annals of Neurology*. 2001; 49:125-9.
9. **Cullen, KM**; O'Connell, C. Degenerating microvessels and reactive astrocytes in Alzheimer's disease: A reinterpretation of the senile plaque. *Neuropathology and Applied Neurobiology*, in press July 2001.
10. **Cullen, KM**; O'Connell, C. Incipient plaques are hypercellular. *Acta Neuropathologica*, in press June 2001.

### **Review Article**

11. **Halliday, G**; Robinson, SR.; Shepherd, C, and Kril, J. Alzheimer's disease and inflammation: a review of cellular and therapeutic mechanisms. *Clinical & Experimental Pharmacology & Physiology*. 2000; 27:1-8.

### **Articles Submitted**

12. **Cullen, KM**; O'Connell, C Evolution of the Alzheimer's disease plaque from active microhaemorrhages to astrocytic scars. *Dementia*, submitted August 2001.
13. **Cullen, KM**, The staging of inflammation in Alzheimer's disease cortex I. *Neurobiology of Disease*, submitted July 2001.

### **Conference Presentations**

1. **Broe, GA**; Halliday, GM; Creasey, H; Corbett, A; Bennett, HP; Grayson, DA; McCann, H, and Kril, JJ. White matter lesions and dementia. 16th Congress Int Assoc Gerontology. 1997.
2. **Halliday, GM**; McCann, H; Brooks, WS, and Broe, GA. Inflammation in Alzheimer's disease: anti-inflammatory medications increase post-mortem neuropathology. 16th Congress Int Assoc Gerontology. 1997.

3. **Broe, GA; Corbett, AJ; Bennett, HP; Brooks, WS; Kril, JJ; Halliday, GM, and Grayson, DA.** White matter lesions, cognitive decline and dementia: a 6-year follow up. 6th Int Alzheimer's Disease Meeting. 1998.
4. **Brooks, WS; Grayson, DA; Nicholson, GA Vale M; Martins, RN; Creasey, H; Waite, LM, and Broe, GA.** APOE-E4 predicts, but anti-inflammatory drugs do not prevent, incident Alzheimer's disease in an elderly community sample. *Neurobiology of Aging*. 1998; 19:S140.
5. **Brooks, WS; Grayson, DA; Nicholson, GA Vale M; Martins, RN; Creasey, H; Waite, LM, and Broe, GA.** APOE-E4 predicts, but anti-inflammatory drugs do not prevent, incident Alzheimer's disease in an elderly community sample. *Aust NZ J Med*. 1998; 28:497.
6. **Kril, JJ; Halliday, GM; McCann, H, and Broe, GA.** Small vessel pathology in probably Alzheimer's disease. *Proc Aust Neurosci Soc*. 1998.
7. **Milward, EA; Grayson, DA; Creasey, H; Janu, MR; Brooks, WS, and Broe, GA.** Anaemia associates with vascular dementia but not Alzheimer's disease. *Proc Aust Neurosci Soc*. 1999
8. **Milward, EA; Grayson, DA; Creasey, H; Kyngdon; B; Janu, MR; Brooks, WS, and Broe, GA.** Anaemia and dementia in community-dwelling Australian elderly. *Aust Carer's Assoc/Aust Ass Geront*. 1999

### ***Key Findings***

Three findings of the studies reported from the ADI stand out. They are distinct but complementary:

#### **1. The protective effect of NSAIDS is not dose related (Broe et al. 2001)**

The team led by GA Broe at Concord Hospital re-analysed their growing body of data yielded by the Sydney Older Persons Study. By both extending the length of this study to over 10 years, and re-designing their analysis, they confirmed their original 1990 finding (that the incidence of AD is inversely related to NSAIDS), and extended it by showing that the effect is not related to dose of NSAIDS. The implication of this finding is that the protective effect may not be related to the anti-inflammatory action of the NSAI drugs, but to some other action. The nature of that 'other' action is now a key question. One possibility, still speculative, arises from the well-established action of some NSAIDS, particularly aspirin, in maintaining the integrity of small vessels, the capillaries of the brain.

#### **2. NSAIDS do not reduce the pathology usually associated with Alzheimer's disease. (Halliday et al., 2000).**

This was a surprising negative finding. In the latter part of the 20<sup>th</sup> Century neuropathologists had come to regard two features of the dementing brain as characteristic (and to some workers) definitive of Alzheimer's disease. These are known as 'plaques' and 'tangles'. Alzheimer had described plaques in his original (1911) paper, and he described a third pathology, the presence of cells which we would now call 'active' microglia, a feature of inflammation. This aspect of the pathology of Alzheimer's disease was neglected until the late 1980's. Halliday and colleagues' study is a uniquely detailed assessment of brains (obtained largely from the cohort of patients followed for many years by the Concord group) whose cognitive history was well documented. In these patients the use of NSAIDS correlated with better cognitive status of the patients, but not with any lessening of plaques, tangles or markers of inflammation. These data confirm the prior studies (now about 20) which report a beneficial effect of NSAIDS on cognitive function in the aged. They suggest that the action of NSAIDS is not to reduce the plaques and tangles which many regard as

definitive of Alzheimer's disease, and also not to reduce inflammation. They suggest that some other pathology is important for cognitive function.

### 3. The early pathology of AD may be microvascular (Cullen, 2001)

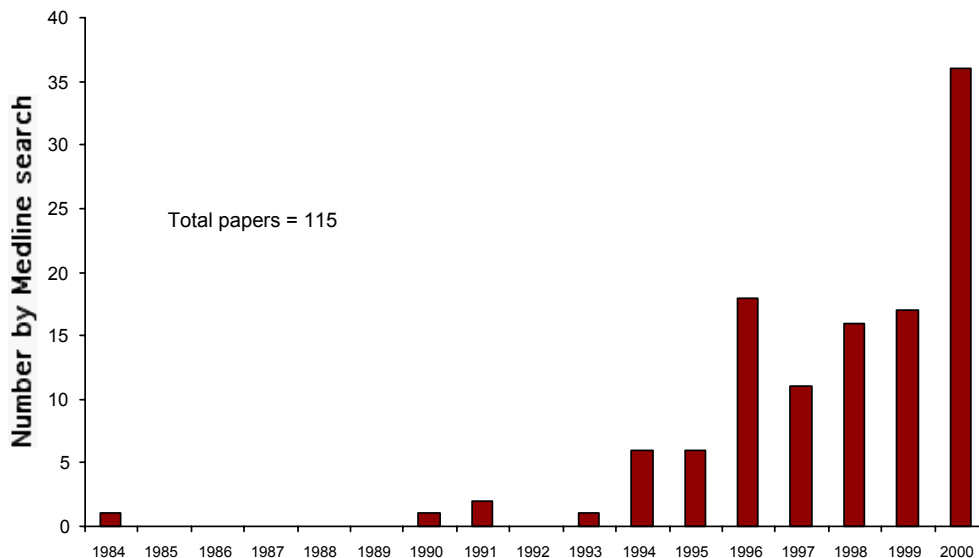
Dr. Cullen's work has also addressed the neuropathology of Alzheimer's disease, but looked at the earliest stages of the cortical lesions which occur. The feature which her papers highlight is that, the earliest lesions always form around a small blood vessel. This is a novel hypothesis/finding, which will receive a lot of analytical attention. Its implication, that the degenerative changes which cumulatively cause dementia centre on blood vessels, complements the two other Sydney findings. NSAIDS may protect against dementia by stabilising the small blood vessels of the brain.

#### *Relationship to the Field*

World-wide, the literature exploring the relationship between Alzheimer's disease and inflammation has grown exponentially since 1996, when the ADI was launched (Figure 1). The Australian contribution to this literature amounts to approximately 15 papers, thus about 13% of the total. Major parts of this literature, particularly the step-by-step demonstration of inflammatory markers in Alzheimer's brains, have been generated in the USA and Europe. The Australian part of that literature, all from Sydney, has made the distinctive contributions identified above.

This line of enquiry is still, by any criterion, unfinished. The initial correlations which inspired it have been extensively confirmed. Neuropathologists have demonstrated inflammatory processes to be as reliable a feature of Alzheimer's disease as plaques or tangles. Initial prospective trials of NSAIDS have reported positive results; extensive clinical trials are under way. The mechanistic analysis – how NSAIDS stabilise cerebral function – is still a controversial and exciting field. This is where the *Alzheimer's Disease and Inflammation Initiative* has made a particular contribution.

**Publications on 'Alzheimer's disease' and 'inflammation'**



I believe I can report to my fellow Trustees, to those who served on the Scientific Advisory Committee and to those who have supported us, that the Fund's Alzheimer's disease and Inflammation Initiative was timely, focussed and, given our resources, was successful and influential.